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Current Drug Repurposing Strategies in Treatment of COVID-19

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Abstract : Drug repurposing is the process of finding the new uses of existing drugs. It is one of the emerging methods involved in selecting a molecule for diseases which are communicable and can spread in the general population at a faster pace. The method is selected over conventional drug discovery methods because it is a faster way to bring an existing molecule for a different disease. Ever since COVID-19 pandemic has emerged worldwide use of repurposed drugs has become an important toll to tackle this viral disease. This review is a study of the varous stargegies of drug reprposing for the treatment of COVID-19.
Keywords : COVID-19, drug repurposing, viral disease.

Introduction:

In early December 2019, the first pneumonia case of unknown origins was identified in China later it came to know that, it was caused by a virus called coronavirus. Corona viruses (CoVs) are enveloped, positive-sense, single-stranded RNA viruses that belong to the genus betacoronaviruses. The coronavirus disease 19 (COVID-19) is a highly transmittable and pathogenic viral infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[1, 2]. This deadliest disease was originated from Wuhan, China in December 2019 and has enormously spread in all over the world[3]. So far, COVID-19 has affected more than 43,000 patients in 28 countries/regions and has became a major global health concern [4,5].

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Coronaviruses (CoVs) are a family of single stranded, with a crown-like appearance (*coronam* is the Latin term for crown) due to the presence of spike glycoproteins on the envelope. Coronaviruses are under four genera: alphacoronavirus (a-CoV), betacoronavirus (b-CoV), gammacoronavirus (c-CoV), and deltacoronavirus (d-CoV). For many reasons yet to be explained the virus can cross barriers can cause illness ranging from common cold to more severe diseases. Thus, SARS-CoV-2 belongs to the betaCoVs category which is round or elliptic and often pleomorphic form with a diameter of approximately 60–140 nm [6,7].

The principle transmission of the CoVID-19 was assumed to be creature to-human transmission but subsequent cases were not related with this mechanism [8]. It was transmitted from human-to-human, through the respiratory course, coughing and sniffling without covering the mouth[9].

Symptoms develop 2 to 4 days after inoculation, but about 30% of the volunteers who excrete virus had no associated illness. The most common symptoms were fever, dry cough, fatigue, shortness of breath. Some additional symptoms, such as running nose, sore throat, headache, body aches and diarrhoea. As, the disease gets into the final stage the symptoms also gets adverse and they were respiratory failure and severe pneumonia[9]. People with other medical conditions (such as asthma, diabetes, or heart disease), were more vulnerable to the attack.

In December 2019, atypical pneumonia cases emerged in Wuhan, China, with clinical presentations consistent with viral pneumonia[10]. On January 2020, The total cases has raised to 7700 and a death toll of 170. Moreover, 75 countries worldwide got infected. As of March 4, 2020, the total number of confirmed cases of COVID-19 has risen to 95,075 with 3,252 total deaths and 51,156 recovered cases [11].

Although there is no known cure for corona virus, healthcare providers are attempting to repurpose antiviral approved to treat other viral infections such as influenza, HIV, and Ebola [11]. Drug repurposing (also commonly referred to as drug repositioning) is a drug development strategy used to identify novel uses for existing approved and investigational drugs outside of their original indication [12].

Antiretroviral

Drugs are used to treat HIV have been used and are currently being investigated for the treatment of SARS-CoV-2 Ritonavir is currently being investigated in clinical trials in combination with other drugs, including danoprevir, oseltamivir, umifenovir, and darunavir [13]. The first antiviral to be approved for the treatment of covid-19 by china was favilavir. It was approved after it showed a good pharmacological and toxicological profile in clinical trial of 70 patients [14].

Antimalarial

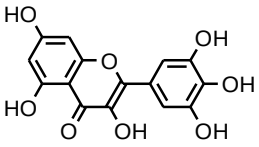
Chloroquine, an anti-malarial drug with anti-inflammatory properties, was authorized by China's National Health Commission for the treatment of pneumonia associated with COVID-19. It was effective against SARS-CoV-2 in vitro[15].

Vaccines

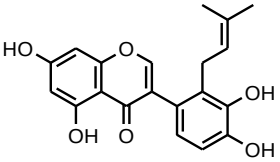
Since vaccines are a cornerstone of disease prevention, various pharmaceutical companies are actively collaborating to pioneer vaccines for the prevention of COVID-19. Moderna Therapeutics has developed mRNA-1273, a vaccine currently under investigation in Phase I clinical trials. INO-4800, an experimental vaccine being developed by Inovio Pharmaceuticals, is in the preclinical stages of investigation[16].

Current Drug repurposing studies:

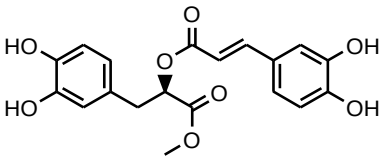
Muhammad et. al., reported that viral - 3 - chymotrypsin like cysteine protease (3cl pro) enzyme which controls the virus replication cycle is an important target in drug discovery approach. They constructed a 3D homology model and screened it against 32,297 medicinal plants library. It revealed that Isoflavones, Myricitrin and methyl rosmarinate are top three phytochemicals in screening, showing a docking score of -16.35, -15.64 and -15.44 respectively [17].



Myricetin



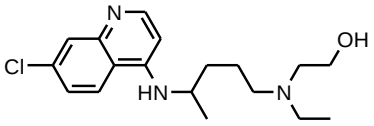
5,7,3',4'-Tetrahydroxy-2'-(3,3-dimethylallyl) isoflavone



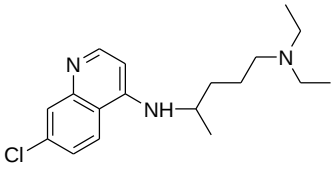
Methyl Rosmarinate

Xueting et al reported that immunomodulatory response of Hydroxychloroquine can be useful in controlling the cytokine storm caused by SARS CoV-2. Physiologically based pharmacokinetic model were used with 5 different dosing regimens and it was found that hydrochloroquine (EC_{50} = 0.72 μM) is more potent than chloroquine (EC_{50} = 5.47 μM) with a loading dose of 400 mg and maintaina

nce dose of 200 mg twice daily[18].

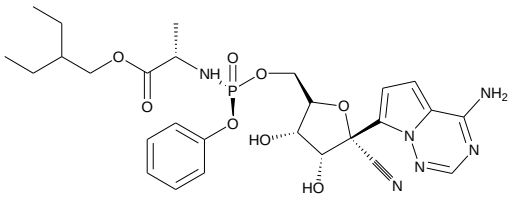


Hydroxychloroquine



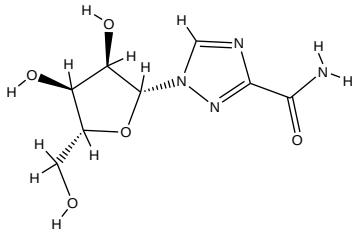
Chloroquine

Manli et al demonstrate that remedisivir and chloroquine are effective against SARS CoV-2 (2019 - nCoV). They reported that remedisivir has EC_{90} value of 1.76 μM against 2019 - nCoV in Vero E6 cells and the study also reported that the drug has virus inhibition activity in Human liver Cancer Huh - 7 cells. It is also studied that chloroquine functioned at both early and past stages in Vero E6 cells having an EC_{90} value of 6.90 μM which can be clinically achieved by 500 mg dose [19] .

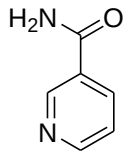


Remedisivir

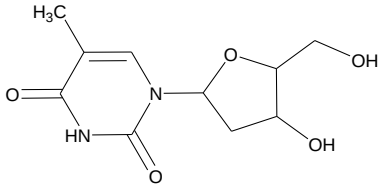
Manli et al reported that effect of different drug on SARS CoV-2 main protease. Use of molecular modelling, virtual screening docking, sequence comparison and phylogenetics to investigate. The identity match up with 96.061% and 51.81% with SARS and MERS coronavirus and found that ribavarin, a drug used against SARS CoV can be used along with telbivudine, vitamin B12 and nicotinamide in treatment of COVID 19[19] .



Ribavarin



Nicotinamide

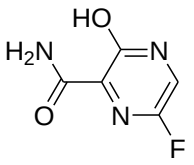


Telbivudine

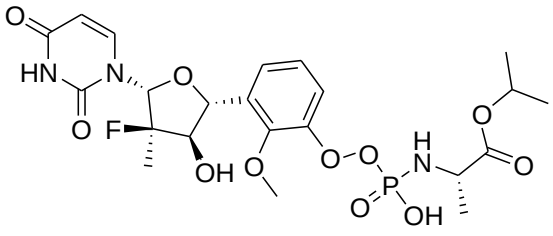
Fantini et al reported a new mechanism of action for anti-malarial drug chloroquine and Hydroxychloroquine. The attachment of viral spike to ACE2 receptor is a main system in attaching virus to cell surface. They identified a new binding domain at N-terminal with facilitating the contact with ACE2 receptor. The study shows that the chloroquine and Hydroxychloroquine are bind to sialic acid and gangliosides with more affinity and thus viral spike would not bind to gangliosides. Thus can be used as drugs against SARS CoV-2[20.]

Junsong et al studied proteolytic processing of the SARS-CoV S protein is essential for the virus entry and fusion. Many cleavage sites of the relevant exogenous protease including cathepsin L and TMPRSS2 involved in the proteolytic processing of the SARS-CoV S protein. Because cathepsin L has been identified as a target of teicoplanin, it is important to identify whether the cleavage site of cathepsin L exists on the 2019-nCOV S protein. After alignment they found that the cleavage site of cathepsin L is well conserved between the SARS-CoV and 2019-nCoV S protein, suggesting that cathepsin L could participant in the 2019-nCoV entry and fusion. It was found that teicoplanin acted specifically as a 2019-nCoV entry inhibitor in dose dependent manner It demonstrated an IC_{50} of 1.66 uM for its inhibitory effect on HIV-luc/2019-nCoV-S pseudo viruses [21].

Deyin studied the antiviral efficiency of FDA approved remdevisir (RDV, GS – 3754) and flavipiravir (T-705). They also found that two compounds CQ (EC_{50} value = 1.13 μmol/L; CC_{50} > 100 μmol/L, SI > 88.50) and RDV (EC_{50} = 0.77 μmol/L; CC_{50} > 100 μmol/L; SI > 129.87) potently blocked virus infection at low-micro molar concentration and showed high selectivity index (SI). RDV is a adenosine analogue prodrug which is incorporated in nascent chain of RNA virus which results in pre-mature termination in RNA synthesis .It shows broad spectrum of antiviral activity in SARS- CoV and MERS viruses. However RDV clinical effectiveness and clinical safety is to be investigated [22].



Favipiravir



Remdesevir

Abdo studied that through their findings through sequence analysis, docking and modeling the model of COVID-19 RdRp is 97% sequence similar to SARS. The COVID -19 is the member of the *betacoronavirus*

similar to MERS and SARS .The compounds IDX-184 , sofosbuvir, ribavirin are the nucleotide derivative compounds shows the binding with COVID -19 and SARS HCOV with high energy which shows the possibility of great efficacy on new emerging viruses. The half-maximal effective concentration (EC_{50}) for Ribavirin against COVID-19 is 109.5 μM [23].

Christian et al studied the antiviral activity of chlorquine on RNA viruses as diverse as HIV, polio, chikungunya, influenza, hepatitis, nipah, Ebola . They reported that both chlorquine and anti viral drug remidevisir inhibits SARS-COV-2 . Chlorquine inhibits early stage of viral cycle by interfering the cell surface receptor. Chlorquine also impair with the early development of viral cell by interfering pH dependent endosome mediated cell entry [24].

Leon et al studied that Ivermectin the anti parasitic agent shown the antiviral activity on broad range of viruses. In vitro conditions they used cell culture viral infection techniques to check the activity and found that the significant amount of reduction in RNA virus SARS COV-19 showed inhibition in his RNA Synthesis. They infected cells with SARS-COV-2 with addition to 5 μM of Ivermectin which showed reduction by ~5000 folds of RNA in 48 hrs [25].

Wang et al conducted a study on efficacy of remdesivir and chloroquine in inhibiting 2019-nCoV. Recently, remdesivir has been recognized as a potent antiviral drug against a large variety of RNA viruses (including SARS / MERS-CoV5) in cultivated cells, mice and non-human primate (NHP) models. Currently it is undergoing clinical research to treat Ebola virus infection [26].

Kruze proposed that blocks entry in 2019-nCoV using a soluble version of the viral receptor, angiotensin-converting enzyme 2 (ACE2), fused to an immunoglobulin Fc domain (ACE2-Fc), providing a neutralizing antibody with peak breath to prevent any viral escape, while also helping recruit the immune system to create lasting immunity. The ACE2-Fc therapy will also complement reduced ACE2 levels in the lungs during infection, thereby directly addressing pathophysiology of acute respiratory distress as a third mechanism of action. An alternative RBD-Fc fusion 2019-nCoV may also be sought if in one molecule one wanted the dual role of receptor blocking and vaccination [27].

Zhang et. al., demonstrated that Teicoplanin, a trimeric glycopeptide antibiotic on the surface of CoVs, has already been shown to be effective in the treatment of Gram-positive bacterial infections, especially in staphylococcal infections, against numerous viruses such as Ebola, influenza viruses, flaviviruses, hepatitis C viruses, HIV viruses and coronaviruses such as MERS-CoV and SARS-CoV. The study performed indicates that in the early stage of the viral life cycle in the late endosomes, Teicoplanin interferes with the cleavage of S-protein by cathepsin L, thereby preventing the entry of viral RNA, subsequent infection, and pathogenesis. Another research performed by the same authors revealed that SARS-Cov-2 retained this operation. The concentration of teicoplanin required to inhibit 50 percent of *in vitro* viruses (IC_{50}) was 1.66 μM, which is much lower than that obtained in human blood (8.78 μM for a daily dose of 400 mg). These preliminary results will now be confirmed by a randomized clinical trial. A dose of 400 mg/day can be administered by 2019-nCoV infection. Owing to its low toxicity, the drug efficacy can be improved by considering doses such as 800 mg/day or 1200 mg/day [28].

Conclusion

Apparently, in addition to current treatment strategies drug repurposing is emerging to be one of the most successful ways to tackle this pandemic. Drugs such as redesivir, hydroxychloroquine, ribavirin, flavipiravir, teicoplanin and other drugs reported in the review can be studied for their efficacy against COVID-19. However, more studies are needed to conform the use of this drugs and its necessary to determine the mechanism of action of these candidates for a better use. As well as the above study suggests screening more drugs using different tools can be helpful in selecting more molecules, that can be used. Lastly these molecules can be helpful in the treatment of COVID-19 if they prove to be effective in animal and clinical studies.

Conflict of interests:

The authors claim no conflict of interests.

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